Peritoneal Dialysis International, Vol. 34, pp. 775–780
doi: 10.3747/pdi.2012.00111

0896-8608/14 $3.00 + .00

BETTER OUTCOMES OF PERITONEAL DIALYSIS IN DIABETIC PATIENTS IN SPITE OF RISK OF LOSS OF AUTONOMY FOR HOME DIALYSIS

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♦ ***Introduction:*** **Diabetes mellitus is a leading cause of chronic renal failure, challenging therapy strategies. Patients with diabetes may benefit from peritoneal dialysis (PD) but higher technique failure is feared. Our purpose was to critically evaluate clinical outcomes of this modality in diabetics, in order to find quality improvement strategies in these risk patients.**

♦ ***Methods:*** **A registry-based study of 432 incident patients, 23% with diabetes, from a university hospital PD program was performed. Traditional methods (Kaplan-Meier, Cox models) and innovative survival analysis, taking competing risks into account, were performed, as well as exploring the trends in cohorts according to the decade of PD start.**

♦ ***Results:*** **In spite of the detrimental effect of diabetes in patient survival compared to non-diabetics (77%, 52% vs 86%, 71%, at 2 and 4 years, respectively; $p < 0.0001$) the hazard ratio (HR) for death decreased in the more contemporary cohort (0.303, 95% confidence interval (CI) 0.150 – 0.614, $p < 0.001$). It is noteworthy that diabetes was not associated with lower technique survival: 74%, 51% vs 79%, 57%, at 2 and 4 years, respectively (p = not significant (NS)). On multivariate analysis, diabetes was an independent predictor for mortality, but not for technique failure. The hazard ratio (HR) for technique failure also decreased in the more recent cohort (0.566, 95% CI 0.348 – 0.919, $p = 0.021$).**

Among reasons for transfer to hemodialysis, proportion of ultrafiltration failure was similar between groups (26% vs 22%, p = NS), but drop-out due to loss of autonomy occurred more in the group with diabetes (23% vs 5%, $p = 0.004$), mainly due to ischemic stroke. The hospitalization rate was also higher in diabetic patients (1.39 vs 0.84 episodes per patient-year (E/PY), $p = 0.004$) but the peritonitis rate was not increased (0.53 vs 0.61 E/PY, p = NS).

♦ ***Conclusion:*** **PD was an effective long-term renal replacement therapy in diabetics, without higher rates of technique failure, ultrafiltration failure or peritonitis. Better outcomes were achieved in the contemporary cohort. The menace of autonomy loss due to stroke and higher hospitalization rates enhance the need for assisted PD strategies and better control of comorbidities.**

Perit Dial Int **2014; 34(7):775–780** **www.PDIConnect.com**
epub ahead of print: 02 Jan 2014 **doi:10.3747/pdi.2012.00111**

KEY WORDS: Diabetes; peritoneal dialysis; outcomes.

The incidence and prevalence of diabetes mellitus (DM) is estimated to continue to rise worldwide (1,2). Diabetic patients face the worst survival (3) both on hemodialysis (HD) and peritoneal dialysis (PD) and represent a challenge to the healthcare team. Debate considering which dialysis modality confers better survival to diabetics still remains, with conflicting reports (4,5).

In the earlier days of PD, diabetic status was a factor in choosing the technique due to the importance of better hemodynamic stability, few episodes of hemorrhagic ocular complications and the feasibility of elective intra-peritoneal insulin. Avoidance of vascular access complications and benefits of the preservation of residual renal function were also relevant. However, today many clinicians fear proposing PD to their diabetic patients because of a presumed higher risk of peritonitis, ultrafiltration failure, metabolic and nutritional deleterious consequences, even though myths might be stronger than facts (6–9).

We undertook this study to analyze the long-term PD treatment of diabetic patients, investigating achieved patient and technique survivals, causes of drop-out, and rates of peritonitis and hospitalization, as well as the trend of survival in cohorts of patients according to the period of PD start. Moreover, a more accurate methodological statistical method was applied to analyze major outcomes facing competing events such as access to transplantation or change of modality.

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Received 8 May 2012; accepted 12 May 2013.

PATIENTS AND METHODS

We retrospectively reviewed the registry data of consecutive adult incident PD patients, in a University Hospital PD Unit – Hospital de Santo António, Porto –, admitted from October 1985 through June 2010. Data included demographic and clinical information prospectively collected as an instrument of continuous quality control in the Unit. Seven of the 439 incident patients were excluded from this analysis: 4 because of missing data and 3 who were lost to follow-up after transfer to another center. We then considered a total population of 432 patients, 11,640 months at risk. The diabetic group consisted of 101 patients (23.4%), of whom 50 (49.5%) had type 2 diabetes.

Basal data included demographics, reason for PD (option/vascular access failure), previous renal replacement therapy (RRT) [PD-first, HD, renal transplantation (RT)] and previous total time on RRT. Survival analysis focused on patient and technique survival. Death within 30 days after transfer to HD was assigned to PD. Causes of death were grouped into cardiovascular, infection related to PD technique, infection not related to PD technique, other and unknown. Causes of transfer to HD were grouped into infection (peritonitis, tunnel and exit-site infection), inadequate dialysis (dose/ultrafiltration failure), loss of autonomy for technique, psychosocial (PD burn-out/logistic) and abdominal complications (catheter and mechanical problems, acute abdomen).

Peritonitis and hospitalization episodes were registered for each patient; global rates for groups with DM and without DM were calculated, presented as episodes/patient-year (E/PY).

STATISTICAL ANALYSIS

Continuous variables data were presented, according to the distribution, as mean and standard deviations or as median and inter-quartile (IQ) ranges and compared between groups using student *t*-test and Mann-Whitney U test respectively. Categorical variables were expressed as absolute and relative frequencies and chi-square test was applied to compare proportions between diabetic and non-diabetic. For survival analysis, the Kaplan-Meier log-rank test and the Cox proportional hazard model were used in order to compare our results with those of previous studies in this area. These outcomes were also explored according to diabetes type 1 versus type 2. Additionally, survival analysis taking competing risks into account was used to report patient and technique survivals. For patient survival, the event of interest was death, and both RT and transfer to HD were considered as competing events. For technique survival, the event of interest was transfer to HD, and both death and RT were considered competing events. Cumulative incidence, defined as the probability that an individual will experience a specific event by time t, was determined. A Gray's test was used to compare patient and technique survival between subgroups. Multivariate models were used to analyze death and the technique failure hazard ratio (HR) according to the period of PD start (period 1: 1985 – 1994; period 2: 1995 – 2004; period 3: > 2004). Poisson models were applied to compare rates of peritonitis and hospitalization.

The statistical analyses were performed using SPSS, version 17.0 (SPSS Inc., Chicago) and R. Significance was assumed at a p level less than 0.05.

RESULTS

PATIENT CHARACTERISTICS AT BASELINE

Characteristics at admission to the PD program of the total population and the comparison between diabetic and non-diabetic patients are presented in Table 1. Age, percentage of patients older than 65 years, gender, reason for PD and previous RRT technique did not significantly differ between groups. It is noteworthy that the diabetic group had a significantly lower RRT vintage, when compared to the counterpart group [33 months (15 – 99) vs 75 months (23 – 125); $p = 0.05$]. In addition, PD represented the first RRT modality in more than half of the diabetics (64%).

PATIENT AND TECHNIQUE SURVIVALS AND CLINICAL REASONS FOR DROP-OUT

Median follow-up time for the entire population was 20.7 months (IQ range 7.5 – 38.3). At the end of the study, a total of 360 patients discontinued PD treatment, 89 (88%) diabetics and 271 (82%) non-diabetics without major differences in cause of death or transfer to HD among the groups (Table 2).

It is noteworthy that diabetic patients did not show a higher proportion of peritonitis or inadequate dialysis as causes of drop-out. However, loss of autonomy for self-care dialysis was a relevant cause in patients with DM (22.9% vs 5.2% in non-diabetics; $p = 0.004$), mainly due to ischemic stroke (4 cases). Severe peripheral arteriopathy (2 cases), frailty after myocardial infarction (1 case) or progressive diabetic retinopathy (1 case) were also causes of loss of capacity for auto-dialysis in diabetics. On the other hand, in the non-diabetic group the causes of loss of autonomy as a reason for drop-out included

TABLE 1
Characteristics of Diabetic and Non-Diabetic Patients at Baseline

	Total	Diabetics	Non-Diabetics	*p*
n (%)	432 (100)	101 (23.4)	331 (76.6)	-
Age (mean, years)	48.5±15.7	49.7±15.9	48.2±15.7	NS
Elderly (*n*, %)	70 (16.2)	18 (17.8)	52 (15.7)	NS
Male (*n*, %)	166 (38.4)	47 (46.5)	119 (36.0)	NS
Previous RRT				NS
PD-first (*n*, %)	233 (53.9)	65 (64.4)	168 (50.8)	
HD (*n*, %)	148 (34.3)	26 (25.7)	122 (36.9)	
Transplantation (*n*, %)	51 (11.8)	10 (9.9)	41 (12.4)	
PD by option (*n*, %)	240 (55.6)	57 (56.8)	183 (55.4)	NS
RRT vintage (median, months)		33 (15–99)	75 (23–125)	0.05

PD = peritoneal dialysis; HD = hemodialysis; RRT = renal replacement therapy; NS = not significant.

TABLE 2
Causes of Drop-Out in Diabetic and Non-Diabetic Patients

Causes of drop-out	Total (*n*=432)	Diabetics (*n*=101)	Non-diabetics (*n*=331)	*p*
Death	94 (26.1%)	33 (37.1%)	61 (22.5%)	0.012
Cardiovascular	55 (58.5%)	20 (60.6%)	35 (57.4%)	NS
Infection/technique	9 (9.6%)	2 (6.1%)	7 (11.4%)	NS
Infection/non-technique	9 (9.6%)	4 (12.1%)	5 (8.2%)	NS
Other	14 (14.9%)	4 (12.1%)	10 (16.4%)	NS
Unknown	7 (7.4%)	3 (9.1%)	4 (6.6%)	NS
Hemodialysis	151 (41.9%)	35 (39.3%)	116 (42.8%)	NS
Infection	67 (44.4%)	11 (31.4%)	56 (48.3%)	NS
Underdialysis/ultrafiltration failure	35 (23.2%)	9 (25.7%)	26 (22.4%)	NS
Loss of autonomy for technique	14 (9.3%)	8 (22.9%)	6 (5.2%)	0.004
Psychosocial	8 (5.3%)	1 (2.9%)	7 (6.0%)	NS
Abdominal complications	26 (17.2%)	5 (14.3%)	21 (18.1%)	NS
Renal transplantation	104 (28.9%)	17 (19.1%)	87 (32.1%)	0.016
Renal function recovery	11 (3.1%)	4 (4.5%)	7 (2.6%)	NS

NS = not significant.

cachexia (1 case), mental disease (1 case), frailty associated with aging (2 cases) and stroke (1 case).

A lower proportion of diabetics received a renal graft during the follow-up (19% vs 32%; $p = 0.016$).

A Kaplan-Meier analysis showed significantly lower global survival in diabetic patients than their counterparts at 1, 2, 3 and 4 years: 89%, 77%, 67%, 52% vs 93%, 86%, 79%, 71%, respectively ($p < 0.001$). However, considering technique survival, we found similar proportions between groups, also at 1, 2, 3 and 4 years: 84%, 74%, 66%, 51% vs 87%, 79%, 66%, 57%, respectively (p = NS) (Figure 1). When exploring the impact of diabetes on these major outcomes, a significant difference in mortality or drop-out was not found between subgroups of type 1 versus type 2 diabetes. Patient survival averaged 41 ± 3.8 vs 47 ± 6.5 months ($p = 0.96$) and technique survival 37 ± 4.3 vs 54 ± 8.3 months ($p = 0.194$) in type 1 and type 2 diabetes groups, respectively. However, a higher proportion of patients in the type 2 diabetes group suffered from peritonitis and hospital admissions (peritonitis 56% vs 41%, $p = 0.09$; technique related admissions 78% vs 58%, $p = 0.03$; non technique related admissions 52% vs 41%, $p = 0.18$).

In a multivariable analysis (Cox) including diabetes, gender, elderly status (> 65 years), PD after HD and PD after transplantation in the model, DM was an independent predictor for patient mortality (HR 2.3; 95% CI 1.5 – 3.7) but not for technique failure (HR 1.3; 95% CI 0.9 – 1.9).

These results were reproduced after taking competing events into account, as a more appropriate statistical approach. The probability of death and transfer to HD (cumulative incidence) by diabetic status are depicted in Figure 2. The probability of death and transfer for HD by 1, 3 and 4 years after starting peritoneal dialysis was 8%, 20%, 24% and 13%, 26%, 31% respectively. Diabetes was a significant predictor for death on PD ($p < 0.001$), but was not a predictor of technique failure ($p > 0.516$). Also age > 65 was a significant predictor for death, as expected, but was not a predictor of technique failure. Thus, after considering the competing risk of death and access to transplantation, aged patients do not have higher risk of PD technique failure.

By using a multivariate competing risk analysis, it was shown that the hazard ratio for both death and technique failure decreased from the remote to the more contemporary (> 2004) cohort (Table 3). Additionally, the model revealed that PD as first dialysis modality is beneficial in comparison with PD after HD.

PERITONITIS AND HOSPITALIZATION RATES

The global peritonitis rate was similar between diabetic and non-diabetic groups (0.53 vs 0.61 E/PY; p = NS). The global hospitalization rate was significantly higher in patients with DM than in their counterparts (1.39 vs 0.84 E/PY; $p = 0.004$).

DISCUSSION

In line with the current debate concerning the low levels of admission of diabetic patients to PD programs,

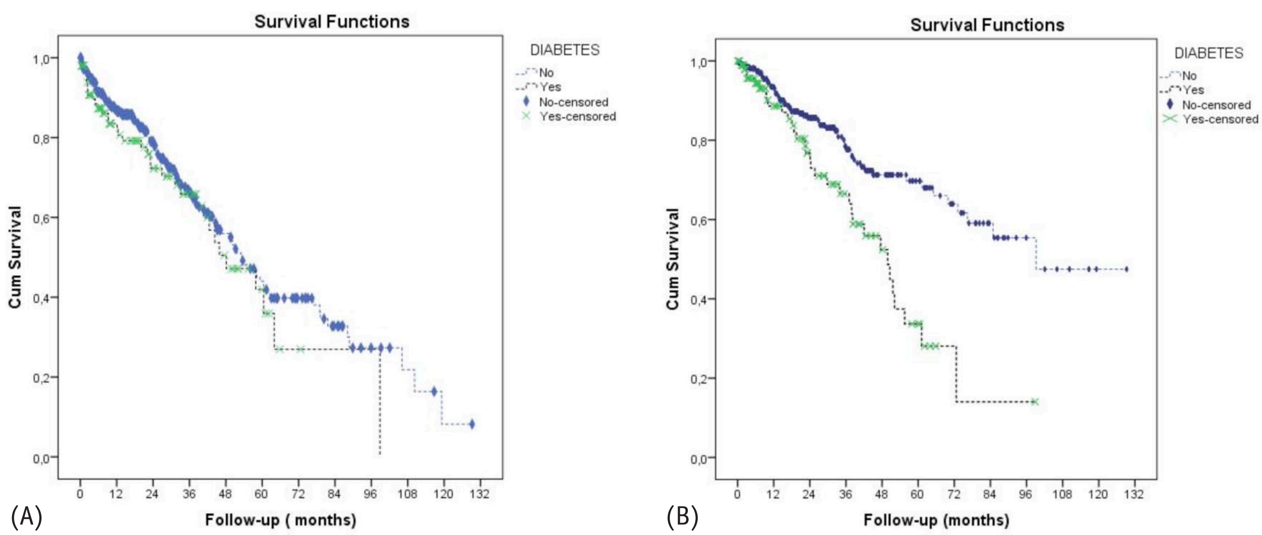

Figure 1 — Kaplan-Meier curves by diabetic status for (A) Technique survival (log rank p=NS) and (B) Patient survival (log rank p<0.0001).

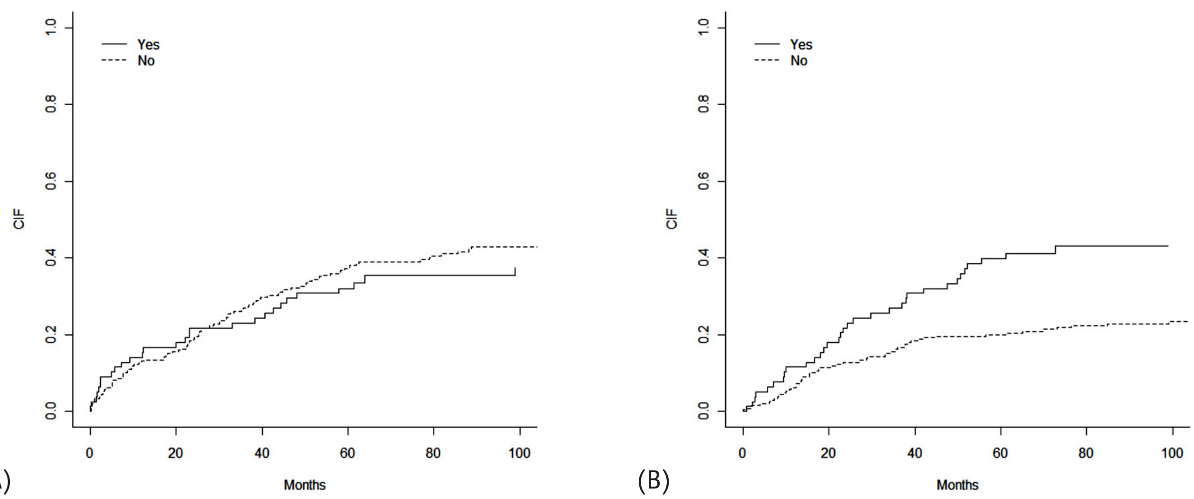

Figure 2 — Cumulative incidence estimates by diabetes status taking competing risks in account for (A) Technique failure (Gray's test p=0.516) and (B) Patient death (Gray's test p<0.001).

TABLE 3
Multivariate Competing Risk Models: Improved Outcomes in Contemporary PD Cohorts

	Death			Technique		
	Exp (coef)	95% CI	*p*	Exp (coef)	95% CI	*p*
Diabetes (Y)	1.926	1.244–2.982	0.003	0.987	0.659–1.479	0.950
Age (>65)	4.117	2.640–6.419	<0.001	0.680	0.418–1.105	0.120
PD after HD*	1.563	1.012–2.414	0.04	1.408	0.987–2.007	0.059
PD after RT*	2.011	0.976–4.144	0.06	1.366	0.836–2.233	0.210
Cohort (1995–2004)**	1.050	0.649–1.698	0.840	0.895	0.611–1.311	0.570
Cohort (=>2004)**	0.303	0.150–0.614	<0.001	0.566	0.348–0.919	0.021

CI = confidence interval; PD = peritoneal dialysis; HD = hemodialysis; RT = renal transplantation.
*PD first group.
** Cohort 1985–1994.

our study adds a favorable report of long-term treatment of diabetic patients with PD. By reanalyzing the outcomes in this high-risk group of patients with different perspectives and appropriate methodologies, we document contemporary improvements and point to areas of further investment.

Our global patient survival rates in the DM group compare favorably with data from the EDTA registry (3) and the USRDS 2010 (1). Focusing on a population that mimics the average age of our treated patients, in the French PD registry, DM patients aged 50 – 60 years had lower three-year patient and technique survivals, reported as 59% and 34%, respectively (10). Better results are achievable with contemporary PD prescription (11). We documented in our study that the cohort that began PD after 2004 showed lower hazards for both death and technique failure in a multivariate analysis. The innovative additional methodological approach, taking into account competing risks events, constitutes an added value of this study. Access to RT is a relevant competing event and in commonly reported survival analysis this has not been taken into account (12). RT was a major cause of drop-out in our study, lowest in diabetic patients when compared to non-diabetics. This current approach updated coherently the classical Kaplan-Meier results.

As expected, in our population, DM was associated with higher mortality (especially cardiovascular) and hospitalization rates. Baseline comorbidity and a higher rate of previous cardiovascular events in diabetics may explain this difference (11,13). Other reasons might be the variations in fluid homeostasis and corporal composition in diabetic patients, as fluid overload is the main cause of cardiovascular death in end-stage renal disease patients, and fluid control is potentially more difficult in PD diabetic patients (5), especially after losing residual renal function.

Despite the higher mortality of diabetics whichever the modality, we did not find significantly more deaths or PD failure in the type 2 DM group. In fact, type 2 DM patients, particularly older female patients, could present more cardiovascular complications associated with obesity, inflammation and atherosclerosis. On the other hand, younger type 1 DM patients often suffer from difficult glycemic control and hypervolemia. Therapy skills, including elective icodextrin and automated peritoneal dialysis (APD) prescription while avoiding glucose load might have conditioned our favorable results (14).

Our study showed a similar rate of technique failure between groups, refuting the association of diabetes with more peritonitis or ultrafiltration failure. Instead, a higher proportion of diabetic patients lost capacity for self-dialysis, mainly due to ischemic stroke, an aspect that has not been previously highlighted (15). This can be explained by progressive diabetic micro- and macroangiopathic complications inherent to most of these patients, such as retinopathy, neuropathy and cerebrovascular disease. Our study underlines the importance of careful management of this complication and also calls for assisted PD strategies.

Our study also enabled us to document a major issue: PD represented the first RRT modality in more than half of the group with DM. This finding constitutes a stimulus to offer the benefits of a PD-first approach in these patients (16), especially since our model pointed to a less advantageous effect of PD after HD.

Some limitations in our study are recognized. Extending our results to the population currently in treatment in Western countries is limited by some of its characteristics, such as the age of its population, which is younger than current standards in some countries, the high percentage of patients arriving from another treatment, and the lack of detailed comorbidity data.

However, single-center studies reports are relevant to identify specific center characteristics with impact on patient and technique outcome (17).

To conclude, despite the known detrimental effect of DM on patient survival, improvements were progressively documented up to the contemporary period. The modality is an effective RRT option in diabetic patients, without significantly higher technique failure or peritonitis rate. However, loss of autonomy for self-care dialysis was proportionally higher in diabetics. Furthermore, this study highlights the relevance of continued detailed prospective data collection to internal quality control assessment and external center experience reports. Major outcomes such as mortality and technique survival should preferably be reported by using competing risk analysis in populations with variable access to renal transplantation and modality transfer.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

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